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MEMORANDUM

Date: April 20, 2010

SUBJECT: OXYFLUORFEN: Second Report of the Cancer Assessment Review Committee

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FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

Jessica Kidwell

THROUGH: Mary Manibusan, Co-chair
Jess Rowland, Co-chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Kit Farwell, Toxicologist
RAB IV, Health Effects Division (7509P)

Kathryn Montague
Herbicide Branch, Registration Division (7505P)

The Cancer Assessment Review Committee met on March 24, 2010 to re-evaluate the cancer classification of Oxyfluorfen in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF OXYFLUORFEN (SECOND REVIEW)

PC Code 111601

Final
April 20, 2010

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Kit Farwell, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Lori Brunsman, Statistician

Kit Farwell

Ray Kent

Mary Manibusan , Co-Chair

Karlyn Middleton

Rob Mitkus

Jess Rowland, Co-Chair

P.V. Shah

OTHER ATTENDEES: Kathryn Montague (RD)

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EXECUTIVE SUMMARY

The Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs re-evaluated the cancer classification of oxyfluorfen on March 24, 2010. The Health Effects Division Peer Review Committee previously classified oxyfluorfen as "Category C, possible human carcinogen", in 1989 with a Q1* based on hepatocellular adenomas and carcinomas in male CD-1 mice and a lack of an acceptable rat carcinogenicity study.

Since that time, the registrant has conducted mode of action studies and a framework analysis proposing dual modes of action by activation of the nuclear receptors, PPARα (peroxisome proliferator-activated receptor alpha) and CAR (constitutive androstane receptor).

Kit Farwell of Reregistration Branch VII presented data from the registrant proposal, which was that the hepatocellular tumors involved two modes of action: activation of PPARα (peroxisome proliferator-activated receptor alpha) and CAR (constitutive androstane receptor). The CARC concluded that neither mode of action was supported by the data.

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Oxyfluorfen as "Likely to be Carcinogenic to Humans". This classification was based on the occurrence of treatment-related hepatocellular tumors in male mice and the lack of an adequate carcinogenicity study in a second species. Although there were no mutagenic concerns for oxyfluorfen, the data were inadequate to support a non-mutagenic mode of action for liver tumorigenesis.

The Committee recommended that a linear low-dose quantitative approach (Q_1*) be retained for human risk characterization with extrapolation based on combined hepatocellular tumors in male mice.

The CARC suggests that the registrant consider submitting a chronic/cancer study in the rat as an alternative to additional mechanistic studies.

I. INTRODUCTION

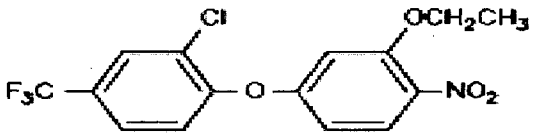
On March 24, 2010, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs evaluated the postulated rodent liver tumor mode of action for oxyfluorfen in light of new mode of action data submitted by the registrant, Dow AgroSciences LLC.

II. BACKGROUND INFORMATION

Oxyfluorfen is a broad spectrum herbicide used to control weeds in corn, cotton, soybeans, fruit, nut trees, and ornamentals and is also registered for residential use as a spot treatment to kill weeds on patios, driveways and similar areas.

Older toxicity studies with oxyfluorfen used technical material of approximately 71% or 85% purity. The newer toxicity studies used a technical material of approximately 98% purity, which is the basis for the current registrations of oxyfluorfen, which are for 97.4% and 99% purity.

Chemical structure:



The Health Effects Division Peer Review Committee met on May 24, 1989 to evaluate the carcinogenic potential of oxyfluorfen (9/24/89 memo from Kerry Dearfield):

> Oxyfluorfen was classified as a Category C oncogen ("Possible Human Carcinogen") based on significant dose-related trends in liver adenomas, carcinomas, and combined adenomas and/or carcinomas in male CD-1 mice. The 1989 Committee concluded that quantification of oncogenic risk was appropriate.

The registrant has submitted data proposing two primary modes of action which involve activation of both PPARα and CAR.

NEW SUBMISSIONS

New submissions relevant for the mode of action evaluation for oxyfluorfen include:

1. Oxyfluorfen: Evaluation of the Mode of Action for Liver Tumors in Male Mice. N. Stagg; D. Eisenbrandt. MRID 47827201. 2009.

> This "framework" document explains the rationale for proposing a MOA based on activation of the nuclear receptors, PPARα and CAR.

2. Analysis of molecular, cellular, and biochemical changes in the livers of male Crl:CD1(ICR) mice treated with oxyfluorfen. M.J. LeBaron, J.A. Murray, H.L. Kan, J. Thomas. MRID 47851601. 2009.

> This study dosed 6 male CD-1 mice per group at doses of 0, 40, 200, 800, or 1600 ppm for 3 or 10 days. Evaluated were gene expression analysis for the AhR signaling pathway (*Cyp1a1, Cyp1a2, Cyp1b1*), CAR/PXR (*Cyp2b10, Cyp3a11, Alas1, NADPH (Por)*), PPARα (*Cyp4a10, Acox1, Cte-1, Pmp-70*), proliferation and apoptosis (*Ccnd1, c-Myc, Bcl-2, Bak-1*), and oxidative stress related signaling pathways (*Cat, Gpx-1, Gstk1, Nox4, Sod2, Ogg1*). Also evaluated were ALT, AST, and GGT liver enzymes; serum cholesterol and triglycerides; and liver weight.

3. Oxyfluorfen: evaluation of hepatic peroxisome proliferation in CD-1 mice. W.T. Stott, S.J. Day, B.L. Yano, *et al.* MRID 46373101. 2003.

> This study dosed 10 male CD-1 mice per group at doses of 0, 40, 200, or 800 ppm for 7 days, 28 days, or for 28 days with a 28-day recovery. Evaluated were S-phase DNA synthesis, acyl co-A oxidase activity, liver weight, electron microscopy, and light microscopy examinations.

4. Evaluation of oxyfluorfen activity in a peroxisome proliferator receptor-alpha reporter assay. M.M. Lebaron, H.L. Kan. MRID 47835802. 2009.

> This *in vitro* study evaluated the ability of oxyfluorfen to bind and activate peroxisome proliferator-activated receptor-α in rat cells.

5. Historical control data which included reporting of hyperplastic nodules, which are now classified as hepatocellular adenomas. The previous historical control data did not include hyperplastic nodules.

III. Evaluation of Carcinogenicity

1. Mouse Carcinogenicity Study

Goldenthal, E. and Wazeter, F. (1977). RH-2915 Technical - Twenty month dietary feeding study in mice. Final reports. International Research and Development Corporation, Mattawan, MI. Laboratory Project Identification: None given, MRID 00037939. Unpublished.

A. Experimental Design

In a carcinogenicity study (MRID 00037939), oxyfluorfen (87.5% a.i.) was administered in the diet to 60 male and 60 female Charles River CD-1 mice at concentrations of 0 (negative control), 0 (ethanol control), 2, 20, and 200 ppm for up to 87 weeks. The corresponding dose levels (adjusted for % a.i.) were 0, 0, 0.3, 3.0, and 33.0 mg/kg/day for males, and 0, 0, 0.4, 4.0, and 42.0 mg/kg/day for females. There was an interim sacrifice of 5 mice/sex for both control groups and the high dose group. One control group received only the basal diet and a second control group received the basal diet mixed with ethanol. The ethanol control group was used because ethanol was used to dissolve oxyfluorfen to mix with feed.

B. Discussion of Tumor Data

There were increasing trends for adenomas, carcinomas, and combined tumor in comparison to both control groups (Table 1). There was a significant pair-wise comparison for combined tumors in comparison to the ethanol control group. The statistical analysis of tumors excludes animals dying before week 53. It is standard procedure for the Office of Pesticide Programs to exclude animals which did not live long enough to develop tumors.

Table 1. Liver Tumors in Male CD-1 Mice Treated with Oxyfluorfen[a]

Liver Tumor	0 ppm untreated	0 ppm ethanol	2 ppm 0.3 mg/kg/day	20 ppm 3 mg/kg/day	200 ppm 30 mg/kg/day
Adenoma	1/47 (2%)	0/47 (0%)	0/44 (0%)	1/44 (2%)	3/52 (6%)
untreated	p=0.0472 *		p=0.5165		
ethanol		p=0.0133 *	p=1.0000		
Carcinoma	1/47 (2%)	1/47 (2%)	0/44 (0%)	3/44 (7%)	5/52 (10%)
untreated	p=0.02.05 *		p=0.5165	p=0.2837	p=0.1272
ethanol		p=0.0205 *	p=0.5165	p=0.2837	p=0.1272
Combined	2/47 (4%)	1/47 (2%)	0/44 (0%)	4/44 (9%)	8/52 (15%)
untreated	p=0.0039 **		p=0.2640	p=0.3073	p=0.0643
ethanol		p=0.0017 **	p=0.5165	p=0.1606	p=0.0226 *

a Mice in 2 ppm group were sacrificed 10 weeks earlier (week 77) than all others.
Significance of trend denoted at control, significance of pairwise comparison with control denoted at dose group. Statistically significant pairwise comparison for combined tumors in the 200 ppm group is by comparison to the ethanol controls. Table excludes mice which died before week 53; first adenoma at week 87, first carcinoma at week 61. * $p < 0.05$ ** $p < 0.01$

C. Historical Controls

The study report for the oxyfluorfen mouse carcinogenicity study was dated 1977 but study dates were not given. The study duration was 87 weeks or 21 months and 3 weeks.

Historical control data in male Charles River CD-1 mice in studies of 20-22 months duration were provided by MPI (successor to IRDC), termination dates 1977 – 1981 (MRID 47827201). At the time of these studies, the term hyperplastic nodules was being used, but those diagnostic criteria are now used to describe hepatocellular adenomas. The previous historical control data did not include hyperplastic nodules.

The incidence of adenomas in the oxyfluorfen study (6%) exceeded the historical control range of 0-5% for adenomas but did not exceed the historical control range for hyperplastic nodules (0-19%). The incident of carcinomas (10%) exceeded the historical control range of 0-8%.

MPI (successor to IRDC) MRID 47887201
Liver Tumors in Male Charles River CD-1 Mice, 20-22 Months

	A	B	C	D	E	F	
Termination	10/77	4/78	5/78	6/78	12/78	8/81	
Route	Stomach tube	Diet	Diet	Diet	Diet	Gastric Gavage	
N	100	90	50	50	75	60	60
Hyperplastic Nodule	8 (8%)	17 (19%	0	0	10 (13%)	0	0
Hepatocellular Adenoma	0	0	2 (4%)	0	0	3 (5%)	3 (5%)
Hepatocellular Carcinoma	2 (2%)	4 (4%)	2 (4%)	0	0	5 (8%)	3 (5%)

The registrant also provided historical control data from Charles River in male CD-1 mice, in 78 week studies from 1987 – 1995. The range of adenomas was reported to be 4-24% and for carcinomas was 0-13%.

The Agency prioritizes the consideration of the concurrent controls and refers to historical control only when and if the concurrent control appear to be extremely inconsistent with previous historical controls. In this case, the concurrent controls are considered more appropriate for comparison to treated animals.

D. Adequacy of dosing

In agreement with the previous CPRC, the CARC determined that the animals could have tolerated a higher dose based on the results of both the carcinogenicity and subchronic studies, which may explain why there was a weak tumor response in this study. However, dosing was considered adequate based upon liver toxicity in the mouse carcinogenicity study and toxicity in the subchronic mouse study described below.

In the carcinogenicity study, there were significantly decreasing trends for mortality with dose. There were very slight increases in alkaline phosphatase (+110%) and SGPT (+77%) in high-dose males. Absolute (+31%) and relative liver weight (+28%) were increased in high dose males in comparison to controls at termination. The liver underwent histopathological evaluation by 3 separate groups of pathologists. Microscopic changes increased in high-dose males noted in the Peer Review document included cytomegaly, karyomegaly, and single cell necrosis (27/55 vs 0/49 or 2/47) in high-dose males when compared to the 2 control groups). A 90-day study (doses of 0, 200, 800 and 3200 ppm) was performed subsequent to this carcinogenicity study to more fully evaluate the dose selection for the long-term study. The LOAEL for this study was 200 ppm based on anemia, elevated liver enzymes (SGPT) in females), increased liver weight, and microscopic liver lesions (single-cell necrosis in females and diffuse hypertrophy in males and females). These effects were also seen at 800 and 3200 ppm, along with increased mortality at 3200 ppm.

2. Rat Carcinogenicity Study

Auletta, C.S.; Rinehart, W.E.; Killeen, J.C.; et al. (1978). A twenty-four month oral toxicity/carcinogenicity study of RH- 2915 in rats. Bio/dynamics, Inc., East Millstone, NJ. Laboratory ID 75-1111A. May 16, 1990. MRID 00083445. Unpublished.

A. Experimental Design

In a combined chronic toxicity/carcinogenicity study (MRID 00083445), oxyfluorfen (85.7% or 82.2% a.i.) was administered in the diet to groups of 50 male and 50 female Long Evans rats at concentrations of 0, 1.0, 20.0, or 400.0 ppm for weeks 1–2; 1.4, 28.3, or 565.6 ppm for week 3–4; 2.0, 40.0, or 800.0 ppm for weeks 5–56 (800 ppm was actually 686 ppm for weeks 6-48); and 2.0, 40.0, or 1600 ppm for weeks 57–104. Based on % active ingredient, doses in males were equivalent to 0, 0.10, 1.94, and 56.96 mg/kg/day, and in females were 0, 0.12, 2.43, and 72.57 mg/kg/day, in the respective dose groups.

B. Discussion of Tumor Data

No treatment-related neoplastic lesions were observed.

C. Adequacy of dosing:

Dosing was not considered adequate for assessing carcinogenicity because treatment-related toxicity was not observed. In addition, dosages were varied during the course of the study and animals received substantially lower doses at the beginning of the study than at the latter part of the study. This study was classified unacceptable for carcinogenicity testing because no treatment-related toxicity occurred in the study and because there were a number of deficiencies in this 1977 study which would not meet current guideline requirements.

IV. Toxicology

1. Background for toxicity

The older toxicity studies with oxyfluorfen used technical material of approximately 71% or 85% purity. The newer toxicity studies used a technical material of approximately 98% purity, which is the basis for the current registrations of oxyfluorfen. There were subchronic rat studies and developmental studies with both the newer and older technical materials which showed that the older technical material was notably more toxic than the newer active ingredient.

Oxyfluorfen and the other diphenyl ether herbicides act by inhibiting protoporphyrinogen oxidase, which is the second-to-last enzyme in chlorophyll biosynthesis. This enzyme is the second-to-last enzyme in heme synthesis, as well (Birchfield and Casida, *Pesticide Biochemistry and Physiology*, 1997). Although oxyfluorfen inhibits heme synthesis, the anemia in various studies was generally mild. As described in the 1997 subchronic rat study, the red blood cell count was normal in this study, but the red blood cell mass was decreased because of the small size of the red blood cells, presumably because of inhibition of protoporphyrinogen oxidase.

2. Subchronic and Chronic Toxicity

Chronic toxicity in mice: In an oncogenicity study (MRID 00037939), oxyfluorfen (87.5%) was administered in the diet to 60 male and 60 female Charles River CD-1 mice at concentrations of 0 (negative control), 0 (ethanol control), 2, 20, and 200 ppm for up to 87 weeks. The corresponding dose levels (adjusted for % a.i.) were 0, 0, 0.3, 3.0, and 33.0 mg/kg/day for males, and 0, 0, 0.4, 4.0, and 42.0 mg/kg/day for females. One control group received only the basal diet; the second control group received the basal diet mixed with ethanol. The ethanol control group was used because ethanol was used to dissolve oxyfluorfen to mix with feed. There was an interim sacrifice of 5 mice/sex for both control groups and the high dose group.

Body weights, body weight gain, and food consumption were similar in all groups. Liver toxicity was shown by increased liver weights, elevated enzyme levels, microscopic liver lesions, and liver tumors. Treatment-related toxicity was more pronounced in males. Absolute and relative liver weights were increased 23-35%, relative to controls, in high-dose animals. Microscopic lesions increased in livers of high-dose animals included hepatocyte necrosis, hepatic regeneration and hyperplastic nodules. Alkaline phosphatase (+110%) and SGPT (+77%) were increased in high-dose males. The NOAEL is 20 ppm for males (3.0 mg/kg/day) and females (4.0 mg/kg/day). The LOAEL is 200 ppm in male (33.0 mg/kg/day) and female (42.0 mg/kg/day) mice, based on liver toxicity (microscopic liver lesions; increased absolute and relative liver weights; and elevated liver enzymes.

Subchronic mouse study: In a 3-month dietary toxicity study (MRID 00117602), oxyfluorfen (72.5%) was administered to Charles River CD-1 mice (15/sex/group) at dietary concentrations of 0, 200, 800, or 3200 ppm for 13 weeks. Doses were equivalent to 0, 32.0,

134.5, or 490.5 mg/kg/day in males and 0, 44.4, 166.6, or 520.9 mg/kg/day in females. Dietary concentrations were adjusted for per cent active ingredient.

Treatment-related mortality in the high-dose group began after 4 days of treatment: 9 male and 2 female deaths during the first 2 weeks of the study were considered treatment-related. Anemia was most evident in high-dose males and females but there were also decreases in hematological parameters in low- and mid-dose males and mid-dose females.

Abnormalities in serum enzymes included elevated SGPT in low-dose females (+295%), mid-dose males (+353%) and females (+638%), and high-dose males (+1177%) and females (+1464%) in comparison to controls. Serum alkaline phosphatase was elevated in mid-dose males (+179%) and females (+109%) and to a greater extent in high-dose males (+1753%) and females (+990%) in comparison to controls. GGT was elevated in mid-dose males and females.

Cholesterol was elevated in low-dose females (+55%), mid-dose males (+76%) and females (+145%), and high-dose males (+282%) and females (+483%) in comparison to controls. Glucose was decreased in high-dose males (-43%) and females (-17%) in comparison to controls. Creatinine was elevated +23% in high-dose males and +18% in high-dose females. Ketonuria occurred in urine from all female treatment groups at week 11. At week 13, urine was darker in color in a dose-related manner in both sexes.

Mixed function oxidase liver enzyme activity as determined by p-nitroanisole demethylation was determined at termination. Activity was increased in mid-dose females and high-dose males and females. Increased liver microsomal protein was also increased in high-dose males.

Absolute and relative liver weights were increased in low-dose (+26%/+22%), mid-dose (+71%/+63%), and high-dose males (+295%/+274%) and in low-dose (+10%/+10%), mid-dose (+62%/+62%), and high-dose females (+245%/+243%).

At necropsy, enlarged livers were seen in 3/5 surviving high-dose males and 11/13 surviving high-dose females; many of these livers were darkened in females. Microscopic lesions in the liver included diffuse hypertrophy (all treatment groups), single-cell necrosis (low-dose females and mid- and high-dose males and females), focal necrosis (mid- and high-dose males), hemosiderosis (all treatment groups), and bile duct proliferation (high-dose males and females). Microscopic lesions of the spleen included atrophy (high-dose males) and red-pulp hyperplasia (all male treatment groups and high-dose females). Bone marrow hyperplasia was present in low-dose males and mid- and high-dose males and females. Vacuolation of the adrenal cortex was present in high-dose females. Thymic atrophy occurred in high-dose males and females.

The NOAEL is < 200 ppm (32.0 mg/kg/day in males and 44.4 mg/kg/day in females), the lowest dose tested. The LOAEL is 200 ppm (32.0 mg/kg/day in males and 44.4 mg/kg/day in females) based upon anemia, elevated liver enzymes (SGPT in females), increased liver weight, and microscopic liver lesions (single-cell necrosis in females and diffuse hypertrophy in males and females).

Chronic toxicity in rats: In a chronic toxicity/carcinogenicity study (MRID 00083445), oxyfluorfen (85.7%) was administered in the diet to groups of 50 male and 50 female Long Evans rats at concentrations of 1.0, 20.0, or 400.0 ppm for weeks 1–2; 1.4, 28.3, or 565.6 ppm for week 3–4; 2.0, 40.0, or 800.0 ppm for weeks 5–56 (800 ppm was actually 686 ppm for weeks 6-48); and 2.0, 40.0, or 1600 ppm for weeks 57–104. Based on % active ingredient, doses in males were approximately equivalent to 0, 0.10, 1.94, and 56.96 mg/kg/day, and in females were 0, 0.12, 2.43, and 72.57 mg/kg/day, in the respective dose groups.

The mortality rate at study termination was 54, 48, 52, and 40% for male and 22, 40, 26, and 20% for females administered the control, low, mid, and high doses, respectively; no treatment-related effect was observed. No treatment-related clinical signs or masses were observed in either sex.

Body weights of high-dose group male rats were similar to those of controls throughout the study. Body weights for low-, mid- and high-dose group females were 9, 7, and 11% less ($p<0.01$ or <0.05) than control weights at most time points during the study. No dose-response relationships were observed for the effects on body weights in females suggesting that the effects were not treatment-related.

No treatment-related effects were observed on hematologic or clinical chemistry parameters evaluated in this study. Absolute and/or relative organ weights in the high-dose groups that showed statistically significant changes relative to control weights (thyroid gland in both sexes and kidney in females at 12 months and brain, pituitary, and spleen in females sacrificed at 24 months) had no microscopic correlates and are not considered toxicologically significant. Gross lesions were not observed in animals sacrificed at 12 or 24 months.

Microscopic changes observed at 12 months included binucleate hepatocytes (6/10), central lobular hepatocyte hypertrophy (7/10), and enlarged hepatocyte nuclei (6/10) in high dose females compared to 0/5 for controls. Similar changes were not seen at the terminal sacrifice, despite the fact that the animals received higher doses during the last 12 months of the study. Therefore the findings at 12 months may be an adaptive effect.

The changes that were statistically increased in the 24-month group were polyploid hyperplasia of the papillary epithelium in the kidney of high dose females (20/40 vs 13/45 controls, $p<0.05$) and cortical cysts in the kidney of mid- and high-dose males (6/25 ($p<0.01$) and 4/40 ($p<0.05$) vs 0/45 for controls). The lack of a dose-response relationship for the changes in males and the high background for the finding in females suggest that the microscopic findings were not treatment related.

The NOAEL is $\geq$ 56.96 mg/kg/day in males and $\geq$ 72.57 mg/kg/day in females, the highest dose group. A LOAEL was not determined. Dosing was not considered adequate for assessing carcinogenicity because no treatment-related effects were observed at any dose. In addition, dosages were varied during the course of the study. Animals received substantially lower doses at the beginning of the study than at the latter part of the study. This study is classified unacceptable because no treatment-related toxicity occurred in the study and because there were

a number of deficiencies in this 1977 study which would not meet current guideline requirements.

Subchronic rat study #1: In a subchronic dietary toxicity study (MRID 00117601), 15 Long Evans rats/group received oxyfluorfen (72.5%) in the diet for 13 weeks. Dietary concentrations of 0, 400, 800 or 1600 ppm in weeks 1 and 2 were increased to 0, 560, 1120, or 2240 ppm in weeks 3 and 4 and were increased to 0, 800, 1600, or 3200 ppm for weeks 5-13. Dietary concentrations were reportedly increased to maintain a constant compound intake and were adjusted for per cent active ingredient. Average compound intake calculated from food consumption over the 13 week period was 0, 51.4, 105, or 234 mg/kg/day in males and 0, 61.1, 124, or 260 mg/kg/day in females for control, low-, mid-, and high-dose groups, respectively. Diets were adequately tested for test material concentration and homogeneity (MRID 42142317).

The only clinical signs were sporadic yellow staining of the ano/urogenital area in high-dose males and females. Body weights were decreased in mid-dose males (-13%) and high-dose males (-21%) in comparison to controls at termination. Food consumption was decreased in mid-dose males (-8%) and high-dose females (-14%). Body weights and food consumption in females were comparable to controls.

A slight anemia was present in mid-dose males (hematocrit depressed -12%) as well as high-dose males (hematocrit depressed -21%) in comparison to controls at week 13 but not at week 4. High-dose females were slightly anemic at week 13 (hematocrit depressed -9%) in comparison to controls. Associated changes in erythrocyte morphology in mid- and high-dose males and females at termination included polychromasia, poikilocytosis, nucleated erythrocytes, target cells, schistocytes, and Howell-Jolly bodies. Platelet counts were slightly decreased in mid- and high-dose groups at weeks 4 and 13 (-11% to -18% in comparison to controls).

Abnormalities in serum enzymes included slightly elevated SGPT in mid-dose males (+27% at week 4 and +33% at week 13) and high-dose males (+31% at week 4 and +94% at week 13) compared to controls. Serum alkaline phosphatase was slightly elevated in mid-dose males (+22% at weeks 4 and 13) and in high-dose males (+32% and 36% at weeks 4 and 13) in comparison to controls. GGT was elevated in high-dose males and females at weeks 4 and 13. Cholesterol was elevated in mid-dose males (+11% at week 4 and +36% at week 13), high-dose males (+33% at week 4 and +56% at week 13), mid-dose females (+26% at week 4 and +22% at week 13), and high-dose females (+39% at week 4 and +56% at week 13). Other clinical pathology abnormalities of less toxicological significance included slightly increased BUN values in all male treatment groups at week 4 and 13, decreased glucose values in all male treatment groups at week 13, increased creatinine in mid- and high-dose males at weeks 4 and 13, and decreased urinary specific gravity in mid- and high-dose males and all female treatment groups

Absolute liver weights were increased in all male treatment groups (+17%, +20%, and +22% for low-, mid-, and high-dose groups) and in high-dose females (+24%) when compared to controls. Relative liver weights were increased in all male treatment groups (+24%, +39%, and +56% for low-, mid-, and high-dose groups) and in high-dose females (+36%) when compared to controls. Other organ weights were comparable to controls.

No gross lesions were attributed to treatment. Microscopic lesions of the liver included diffuse hepatocellular hypertrophy and eosinophilia in all male treatment groups and in high-dose females; hepatic necrosis was seen in 3 high-dose males. Hypertrophy of cells in the zona glomerulosa of the adrenals was seen in all male and female treatment groups. In the kidney, focal basophilia of renal cortical tubules and dilated collecting tubules were seen in high-dose males.

The NOAEL is < 800 ppm (51.4 mg/kg/day in males and 61.1 mg/kg/day in females), the lowest dose tested. The LOAEL is ≤ 800 ppm (51.4 mg/kg/day in males and 61.1 mg/kg/day in females) based upon increased liver weights in males, microscopic liver lesions in males, and microscopic adrenal lesions in males and females. Not all table entries in HED's microfiche copy of the study report were clearly readable; this did not interfere with verifying conclusions reported here, however. Several clinical pathology analyses were not conducted: blood clotting measurements, electrolytes, and SGOT. These deficiencies did not interfere with interpretation of toxicity observed in this study. This study is classified acceptable/guideline and satisfies requirements for a subchronic toxicity study in rats with oxyfluorfen.

Subchronic rat study #2: In this subchronic oral toxicity study (MRID 44933101), oxyfluorfen technical (98.0% a.i.) was administered for 13 weeks to 10 CD rats/sex/dose at dietary concentrations of 0, 500, 1500, 6000, or 10000 ppm (equivalent to [M/F] 0/0, 46.7/50.4, 143.5/150.5, 585.0/643.8, or 1012.1/1058.6 mg/kg, respectively).

There was no treatment-related mortality and food consumption, clinical observations, and gross pathological findings were unaffected by treatment. Principal toxicity included decreased body weights, diuresis, slight anemia, minor changes in other hematological parameters and clinical chemistries, slight organ weight changes, and minor histopathological observations as detailed below. No treatment-related findings were observed in the 500 ppm group.

At 1500 ppm, mean cell hemoglobin concentration and mean cell volume were decreased in males (↓ 10%, each), but were not considered toxicologically significant because other hematological parameters were unaffected. In females, urine volume was increased(↑ 80%) and urine potassium concentration was decreased in males (↓ 43%). These changes were not considered toxicologically significant in the absence of increased water consumption, clinical chemistry changes, or organ weight changes.

At 6000 ppm, terminal body weights were decreased only in females (↓11%). Treatment caused a microcytic anemia in the 6000 ppm and 10000 ppm groups: there was a decreased hematocrit with small erythrocytes and normal RBC count. At 6000 ppm, hematocrits and hemoglobin were decreased (↓12% to 13%) in males and females. Mean cell hemoglobin and mean cell volumes were decreased (↓16% to 19%) in males and females. Platelet counts were increased (↑13%) in the 6000 and 10000 ppm male groups only. Prothrombin time was increased (↑ 46% and 62%) in 6000 and 10000 ppm males only.

Possible renal effects at 6000 ppm included increased urine volume in both sexes (↑ 48-160%), increased urine chloride concentration (↑76-103%), decreased urine potassium concentration (↓ 63-64%), and increased water consumption. Plasma urea (↑ 18%) and creatinine (↑ 13%) were

increased in males only. Relative kidney weights were increased in females (↑ 10%, p≤0.01) only. There was an increased incidence of pigment in cortical tubular epithelium of the kidneys. Possible liver effects at 6000 ppm included increased prothrombin time in males (↑ 46%), and cholesterol (↑ 53%). Relative liver weights were increased in both sexes (↑ 13-28%) at 10000 ppm.

At 10000 ppm, terminal body weights were decreased (males: ↓22%; females: ↓9%). Hematocrits and hemoglobin were decreased (↓ 15-19%) in males and females. Mean cell hemoglobin and mean cell volume were decreased (↓ 18-21%) in males and females.

Possible renal effects at 10000 ppm included increased urine volume(↑ 79-280%,) in males and females and water consumption. Urine sodium concentration was increased in females only (↑ 96%. Urine chloride concentration was increased in males and females (↑ 120-213%). Increases in blood chemistry parameters in males included: urea (↑ 25%); and creatinine (↑ 23%). In females, creatinine(↑ 18%) and relative kidney weights were increased (↑ 12%). Microscopically, an increase in pigment in the cortical tubular epithelium of the kidneys (7/10 vs. 0/10 controls, in males and females) was seen.

Possible liver effects at 10000 ppm in males included increased prothrombin time (↑ 62%), alkaline phosphatase (↑ 25%, p≤0.01), and total cholesterol (↑ 53%, p≤0.01); values in females were comparable to controls. Absolute liver weights were increased in females (↑ 18%), and relative liver weights were increased (↑ 21-26%, p≤0.01) in males and females.

Increased absolute spleen weights were observed in males (↑ 31%) and females (↑ 39%; relative spleen weights were only increased in the females (↑ 47%). This was accompanied by extramedullary haemopoiesis of the spleen (males-8/10 vs. 0/10 controls, females 5/10 vs. 0/10 controls) seen microscopically. Other microscopic lesions in the 10000 ppm group included increases in inflammatory cell in the zona reticularis in the adrenals and single cell necrosis in the zona reticularis in the adrenals.

The NOAEL for this study is 1500 ppm (equivalent to 143.5 mg/kg/day in males and 150.5 mg/kg/day in females). The LOAEL for this study is 6000 ppm (equivalent to 585.0 mg/kg/day in males and 643.8 mg/kg/day in females) based on body weight decrements, anemia, increased urine volume, and increased liver weights. This study is classified acceptable/guideline (§82-1[a]) and satisfies the guideline requirements for a subchronic oral toxicity study in rats.

3. Mutagenicity

Adequacy of data base for Mutagenicity: The acceptable studies performed with the ≥96% test material satisfy the 1991 mutagenicity guidelines and no further testing is warranted.

Tables 2, 3, and 4 show results for 20 genetic toxicology studies with 96-99.7% test material, approximately 72% test material, and a polar fraction. **The newer technical material** (96-99% a.i.) **was tested in 12 genetic toxicology studies, all of which were negative, except for one Ames assay which was positive only at high, insoluble levels**. A second Ames assay with 96%

material was negative. The **older 72% technical material and a polar fraction** were tested in 8 genetic toxicology studies, of which 3 Ames assays were positive, as was a mouse lymphoma study. (See the HIARC report, dated 4/23/01 for more details.)

Table 2 presents summarized findings of the acceptable genetic toxicology assays performed with formulations of oxyfluorfen containing ≥96% of the active ingredient (ai). As shown, samples of 97.1 or 99.7 % ai were negative in the mouse lymphoma assay. Single studies with Chinese hamster ovary (CHO) cells (gene mutation and chromosome aberrations) as well as bacterial DNA damage were also negative with the 99.2 or 97.1% formulations, respectively. *In vivo* studies performed with either 96% (mouse micronucleus and unscheduled DNA synthesis, UDS, in rat hepatocytes assays) or 97.1% (mouse cytogenetic assay) were negative up to or in excess of the limit dose (2000 mg/kg). Only the data from the Ames assays showed conflicting results; the findings were as follows:

Negative up to 7500 µg/plate--no compound precipitation----------99.7%
Positive in TA100 at high insoluble levels (≥1667 µg/plate +S9)----------96%
Negative up to an insoluble dose (5000 µg/plate)----------96%
Negative but currently unacceptable up to 5000 µg/plate; insoluble at ≥1667 µg/plate----------99.2%

It was noted that the Ames assays performed on the 96% test product were conducted by two different contract laboratories and each study consisted of two independent trials. The summary presentation of the results from various test systems with oxyfluorfen purity levels of 96-99.7% indicate that the test material is devoid of mutagenic activity. There are, however, conflicting results for the Ames assays which were not reconciled by testing various lots or purity levels.

Table 3 presents data from the acceptable genetic toxicology studies performed with oxyfluorfen formulations of 71.4-73% ai and Table 4 shows results with the polar fractions of the 72.7% preparation. In agreement with the *in vivo* results for the purified samples, regardless of the percentage ai in the test material, oxyfluorfen had no adverse effect on the chromosomes of two rodent species. Similarly, the lack of activity for the 73% preparation in the *in vitro* UDS assay is consistent with the negative findings for 96% oxyfluorfen *in vivo*. The polar fraction of the test material (derived from RH-2915, lot no. 2-3985, 73% ai) was also negative for UDS *in vitro*. However, samples containing 71.4 or 72.7% ai were confirmed mutagenic for *Salmonella typhimurium* strains TA98 and TA100 either with S9 (both samples) or without S9 (72.7% ai only) at concentrations as low as 250 µg/plate +S9 (TA100). In the absence of S9 activation, mutagenicity was either not reproducible or generally confined to high levels. S9-activated lot no. 2-3985 (72.7% ai) was also mutagenic in the mammalian cell gene mutation mouse lymphoma assay. Although the response was not dose related, increased mutation frequencies were recorded at 1.97 to 40 µg/mL +S9; higher concentrations were insoluble.

A comparative analysis of the different ai percentages showed that attempts to purify the test material were partially successful as indicated by the negative response in the mouse lymphoma assay for the 99.7% formulation (see Table 2). However, despite the data showing that the bacterial mutagenic components could be isolated in a polar fraction (Table 4), as discussed earlier, there were conflicting data for the 96% a.i. samples in the Ames test. It has also been

mentioned that both samples were from the same lot number and that the bacterial assays were independently conducted by two contract laboratories. Nevertheless, one laboratory produced confirmed negative results while the other laboratory reported confirmed evidence of a positive response in *S. typhimurium* strain TA100 at high insoluble S9-activated doses.

CONCLUSIONS: There are no mutagenic concerns for the >96% a.i. which is the level of purity currently used in the product formulation.

Table 2. Genetic Toxicology Profile of Oxyfluorfen **≥96 %** Active Ingredient

Assay	Lot No.	Purity (%)	MRID	Result
Ames	TTF068	99.7	00098421	Neg. to HDT (7500 µg/plate); no ppt.
Mouse Lymphoma	0453	99.7	00098419	Neg; ppt at ≥62.5 µg/mL
Ames [a]	252/1	96	44942801	**Pos. TA 100 at high insoluble doses (≥1667 µg/plate +S9)**
Ames [a]	252/1	96	44933104	Neg to HDT (5000 µg/plate); insoluble at this level
Mouse Micronucleus	P-8	96	44933105	Neg to HDT (2000 mg/kg, ip); cytotoxic to bone marrow
In vivo Rat UDS	P-8	96	44933106	Neg to HDT (2000 mg/kg)
Ames	NA	99.2	44947206	Neg; unacceptable but upgradable
Mouse Lymphoma	NA	97.1	44947202	**Neg; ppt. not reported**
CHO/HGPRT	NA	99.2	44947205	Neg; ppt at ≥50 µg/mL
CHO/Chromo Aberrations	NA	99.2	44947204	Neg; ppt at ≥450 µg/mL
In vivo Mouse Cytogenetics	NA	97.1	44947203	Neg to HDT (5000 mg/kg)
Bacterial DNA Damage/Repair	NA	97.1	44947201	Neg; ppt. at 1000 µg/plate

[a] The two Ames studies were conducted in different laboratories; each protocol required two independent trials.
HDT = Highest dose tested ppt = precipitation ip = intraperitoneal NA = not available

Table 3. Genetic Toxicology Profile. Oxyfluorfen **71-73 %** Active Ingredient

Assay	Lot No.	Purity (%)	MRID	Result
Ames	AMB18-42A	71.4	40992201	**Pos strains TA98 & TA100 at insoluble (≥1600 µg/plate +S9) and soluble (900 µg/plate +S9) doses; weak unconfirmed response -S9**
In vivo Rat Cytogenetics	2-0956	71.4	41873801	Neg to HDT (5 g/kg)
In vivo Rat Cytogenetics	2-3985	72.5	00098418	Neg up to lethal dose (1.19 mg/kg)
Ames	2-3985	72.7	00098420	**Pos. strain TA1537 (≥2500 µg/plate +S9; ≥6000 µg/mL -S9); TA98 (≥500 µg/plate +S9; ≥1000 µg/mL -S9); TA100 (≥250 µg/plate +S9; ≥2500 µg/mL -S9)**; no ppt reported
Mouse Lymphoma	2-3985	72.7	00109283	**Pos. 1.95-40 µg/mL +S9; no dose response; ppt at ≥62 µg/mL**
In vitro UDS Rat Hepato	7530	73	00098423	Neg to cytotox doses (25 µg/mL)

Table 4. Genetic Toxicology Profile of Oxyfluorfen **Polar Fraction**

Assay	Lot No.	Purity (%)	MRID	Result
Ames	2-3985	NA	00098422	**Pos. (only tested TA98) ; 50-7500 µg/plate +/-S9 not dose related**; stronger response +S9
In vitro UDS Rat Hepato	2-3985	NA	00098424	Neg up to cytotox dose (25 µg/mL)

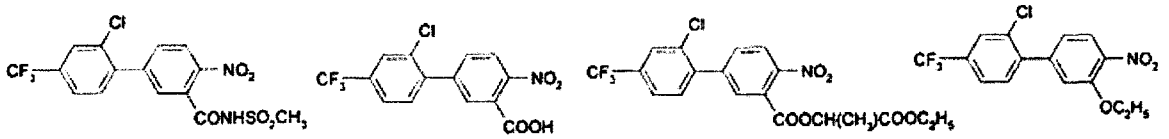
4. Metabolism

Two metabolism studies were available. Oxyfluorfen was rapidly absorbed, extensively metabolized, and rapidly eliminated. Elimination of radioactivity from plasma was biphasic in both low- and high-dose groups (rapid phase = 9-13 hours; slow phase =26-32 hours). More compound was eliminated in the feces (71-87% males, 64-69% females) than in urine (5-10% males, 19-25% females). Bioaccumulation did not occur. In feces, parent compound represented the highest amount of radioactivity. In urine, most compounds were conjugates. Three major pathways include O-deethylation, nitro reduction, and diphenyl ether cleavage.

RH-45469, in which the nitro group was reduced and then acetylated, was a major metabolite in feces, representing 6-22% of radioactivity in both sexes of all dose groups. RH-45289-C, in which the nitro group was reduced, represented 16% of radioactivity in the urine of high-dose females. RH-34800-C, in which the diphenyl linkage was cleaved, was found in urine of males and females at up to 9% radioactivity in the single and repeated low dose groups, but only at

<3% concentrations in the male and female high dose groups. There were 16 other metabolites, mostly <5% radioactivity. See the Appendix for the metabolic pathway.

5. Structure Activity Relationships



fomesafen acifluorfen lactofen oxyfluorfen

Oxyfluorfen is structurally related to 3 other diphenyl herbicides, acifluorfen, lactofen, and fomesafen. The mode of action of rodent hepatocarcinogenesis for these 3 chemicals involves activation of PPARα. Acifluorfen is the main metabolite of lactofen. Up to 10% of fomesafen may be hydrolyzed to yield a carboxylic acid metabolite, thus, fomesafen, acifluorfen, and lactofen may have a common carboxylic acid metabolite. Mouse liver tumors were found in studies with all 4 chemicals but only lactofen had liver tumors in rats (mostly benign).

Structure-activity relationships studies have shown that one of the major structural requirements of most potent peroxisome proliferators is the presence of an acidic functional group (e.g., carboxylic) either in the parent compound or a metabolite (Woo and Lai 2003). Despite structural similarity to the other diphenyl ether herbicides, oxyfluorfen cannot be metabolized to a carboxylic acid metabolite, suggesting that oxyfluorfen is not expected to be a significant peroxisome proliferator (at most weak or marginal based on SAR). Thus, oxyfluorfen is not a good analog of fomesafen-like compounds with respect to PPAR alpha activation as the primary rodent liver mode of action.

6. Summary of Results from Mode of Action Studies

Electron microscopy (28-day study, MRID 46373101, 2003) - Livers from 5 controls and 4 high-dose mice were examined by electron microscopy. Peroxisomes were not increased.

S-phase DNA synthesis (28-day study, MRID 46373101, 2003) - Labeling indices for BrdU infused mice were calculated. Values were variable as shown by the large standard deviations. The labeling index was similar to controls at 40 ppm. At day 7, the mean labeling indices for the 200 ppm groups was similar to controls. With increased duration of treatment, at 200 ppm on Day 28, the labeling index (%) was increased but not statistically significantly. At 800 ppm, labeling index was increased at Days 7, 28, and following recovery in each evaluated hepatic region. Partial recovery was demonstrated. See Table 5.

Table 5. Mean labeling index (%) for hepatocellular S-phase DNA synthesis in male mice.

Day	Dose (ppm)			
	0	40	200	800
Centrilobular				
7	1.49±1.24	0.88±0.56	0.84±0.61	3.40±2.41* (↑**128**)
28	1.43±1.22	1.47±1.75	3.47±1.40 (↑143)	14.91±7.25* (↑**943**)
Recovery Day 28 [a]	2.07±1.02	NT	NT	4.01±2.62* (↑**94**)
Midzonal				
7	1.20±1.27	0.73±0.35	0.81±0.75	2.70±2.44 (↑**125**)
28	1.54±1.55	1.22±0.98	2.66±1.19 (↑73)	13.52±5.93* (↑**778**)
Recovery Day 28 [a]	2.00±1.21	NT	NT	4.10±2.15* (↑**105**)
Periportal				
7	1.31±1.34	0.89±0.49	0.69±0.60	2.83±2.63 (↑116)
28	1.15±0.94	1.41±1.49	2.01±1.00 (↑75)	12.90±5.34* (↑**1022**)
Recovery Day 28 [a]	2.03±1.18	NT	NT	2.43±1.31 (↑20)

MRID 46373101. (% difference from controls). * $p \leq 0.05$. a Treated for 28 days, recovery for 28 days. n=10

Acyl-CoA oxidase assay (28-day study, MRID 46373101, 2003) - Results were variable as shown by large standard deviations, making it difficult to identify an associated increase in acyl-CoA activity due to treatment.. ACO activity was increased at 800 ppm but the standard deviation almost doubles from 200 to 800 ppm, only a minimal increase at 200 ppm but again, is difficult to interpret based on the large variability. Activity returned to control levels following the 28 day recovery period.

Table 6. Mean acyl-CoA oxidase activity (nm/min/mg protein) in male mice (n=10).

Dose (ppm)			
0	40	200	800
Treatment Day 28			
8.02±2.93	8.96±4.03	12.47±8.17 (↑55)	39.76±14.48* (↑395)
Recovery			
6.40±3.08	Not Tested	Not Tested	7.48±6.57

Data from Table 9, pages 54-55 of MRID 46373101. % difference from controls, calculated by reviewer.

Liver histology (28-day study, MRID 46373101, 2003) - No treatment-related effect on the histology of the liver was evident following 7 days of treatment. On Day 28, hypertrophy and vacuolization consistent with fatty change was found in 200 and 800 ppm groups; also at 800 ppm were necrosis, inflammation, karyomegaly, mitotic alterations, and pigment laden macrophages, which are observations more consistent with a cytotoxic mode of action. Karyomegaly and hypertrophy continued at 800 ppm following the recovery period. See Table 7.

Table 7. Selected non-neoplastic hepatic histological findings (# affected/10) in male mice

Non-neoplastic hepatic lesion		Dose (ppm)			
		0	40	200	800
Day 7					
Hypertrophy, hepatocyte, centrilobular/midzonal	Total (slight)	1	0	0	0
Mitotic alteration, hepatocyte, all zones	Total (very slight)	0	0	1	1
Day 28					
Hypertrophy, hepatocyte, centrilobular/midzonal	Total (slight)	3	2	6	10
Vacuolization consistent with fatty change, hepatocyte, centrilobular/midzonal	Total very slight slight moderate	0 0 0 0	0 0 0 0	5 3 2 0	10 3 5 2
Necrosis, individual hepatocyte, centrilobular/midzonal, multifocal	Total very slight slight	0 0 0	0 0 0	1 1 0	9 6 3
Inflammation, subacute to chronic, multifocal	Total (very slight)	0	0	1	6
Karyomegaly, hepatocyte, multifocal	Total (very slight)	0	0	1	4
Mitotic alteration, hepatocyte, centrilobular/midzonal, multifocal	Total (very slight)	0	0	0	5
Pigment-laden macrophages, centrilobular/midzonal, sinusoid, multifocal	Total (very slight)	0	0	1	4
Recovery					
Hypertrophy, hepatocyte, centrilobular/midzonal	Total (slight)	5	NT	NT	10
Karyomegaly, hepatocyte, multifocal	Total (very slight)	0	NT	NT	8
Mitotic alteration, hepatocyte, centrilobular/midzonal, multifocal	Total (very slight)	0	NT	NT	2
Necrosis, individual hepatocyte, centrilobular/midzonal, focal	Total (very slight)	0	NT	NT	1
Necrosis, individual hepatocyte, centrilobular/midzonal, multifocal	Total (very slight)	0	NT	NT	1
Necrosis, inflammation, hepatocyte, focal	Total (very slight)	1	NT	NT	0

Data (n=10) from Table 11 on page 59-62 of MRID 46373101. NT Not tested

PPARα reporter assay (MRID 47835802, 2009) - This test was negative in rat hepatoma cells. Mouse cells were reportedly not available for this assay.

An article in the open literature reported that oxyfluorfen, as well as acifluorfen, were negative for PPARα agonist activity in monkey kidney cells (Takeuchi et al., Tox Appl Pharm 217 (2006) 235–244).

Liver Weight (3 and 10 days treatment, MRID 47851601, 2009) – Mean relative liver weight of 800 ppm males was increased 11.7% after 10 days. In the 1600 ppm group, relative liver weight was increased 11.5% after 3 days; after 10 days, absolute live weight was increased 24% and relative liver weight was increased 26%.

Clinical Chemistries (3 and 10 days treatment, MRID 47851601, 2009) - On day 11, the 1600 ppm group had increased cholesterol and decreased triglycerides compared to controls. The positive controls had both decreased cholesterol and triglycerides. The ALT activities varied widely in each group and had wide standard deviations. See Table 8.

Table 8.
Clinical chemistries fromCrl:CD1(ICR) mice dosed with Oxyfluorfen or positive control for 3 or 10 days.

	AST		ALT		GGT		Chol		Trigl	
ppm	day 4	day 11	day 4	day 11	day 4	day 11	day 4	day 11	day 4	day 11
0	145 ±47	144 ±51	140 ±128	138 ±68	2 ±1	2 ±1	119 ±11	**121** ±13	148 ±33	**138** ±13
40	155 ±33	172 ±69	211 ±30	260 ±249	2 ±16	2 ±1	121 ±16	121 ±13	131 ±31	136 ±44
200	103 ±8	142 ±31	78 ±33	127 ±56	2 ±1	2 ±1	103 ±8	124 ±20	133 ±30	133 ±20
800	157 ±68	114 ±35	145 ±118	85 ±24	2 ±1	2 ±1	117 ±15	131 ±13	107 ±21	126 ±26
1600	145 ±30	168 ±71	82 ±35	272 ±183	2 ±1	2 ±1	116 ±10	**152 *** ±25	112 ±28	**85 *** ±40
Fomesafen 100 ppm	153 ±45	138 ±26	160 ±162	136 ±66	2 ±1	2 ±1	100 ±11	105 ±17	77 ±12	71 ±13
Clofibric 1500 ppm	138 ±33	131 ±48	90 ±42	108 ±68	2 ±1	2 ±1	86 ±20	129 ±20	101 ±16	129 ±35

Positive controls are 100 ppm Fomesafen and 1500 ppm clofibric acid. Chol = cholesterol, Trigl = triglycerides. n=6.. From pages 53 and 54, MRID 47851601, 2009.

Gene Expression study (3 and 10 days treatment, MRID 47851601, 2009)

Gene Expression: PPARα signaling - Oxyfluorfen caused dose-related upregulation of PPAR-α signaling genes. *Cyp4a10* expression was increased at 200 ppm and above after 3 days of treatment (8.30- to 232.8-fold), and at 40 ppm and above after 10 days of treatment (3.70- to 240.6-fold). *Cte-1* expression was increased at 800 ppm and above after 3 days of treatment (7.11- to 14.46-fold), and at 200 ppm and above after 10 days (2.22- to 9.48-fold). *Acox1* expression was increased at 1600 ppm after 3 and 10 days of treatment (4.63-fold and 3.39-fold). The positive controls were much stronger inducers, suggesting that oxyfluorfen is not a strong PPAR-α agonist and is not similar in activity to formesafen. See Table 9.

TABLE 9. PPAR-α signaling (fold increase)[a]

Gene	Oxyfluorfen (ppm)					Positive controls	
	0	40	200	800	1600	Clofibric acid[b]	Fomesafen[c]
3-Day Treatment							
Cyp4a10	1	1.70	8.30	93.00	232.8	746.1	905.4
Acox1	1	-1.15	1.10	2.23	4.63	6.86	4.24
Cte-1	1	-1.28	-1.16	7.11	14.46	18.78	58.98
Pmp-70	1	-1.11	1.04	1.53	2.24	3.24	4.25
10-Day Treatment							
Cyp4a10	1	3.70	14.40	111.5	240.6	523.9	1542.5
Acox1	1	-1.64	-1.67	1.05	3.39	1.47	3.82
Cte-1	1	-1.03	2.22	4.85	9.48	20.33	78.08
Pmp-70	1	1.11	1.30	1.46	1.98	2.58	4.55

a Data were obtained from Text Table 5 on page 31 of the study report. fold = $2^{-\Delta\Delta Ct}$

b Clofibric acid was administered at 1500 ppm. c Fomesafen was administered at 100 ppm

Gene Expression: CAR/PXR signaling CAR signaling was assessed by induction of *Cyp2b10* and the CAR/PXR pathway was assessed with *Alas1, Cyp3a11, and NADPH (Por).*

Treatment with oxyfluorfen caused a dose-related upregulation of *Cyp2b10* at 200 ppm and above after 3 days (4.75- to 67.45-fold) and 10 days (8.29- to 38.67-fold) of treatment (Table 10). Additionally, *Alas1* expression was increased to a lesser extent at 800 ppm and above after 3 days (3.17- to 14.10-fold) and 10 days (2.80- to 15.26-fold) of treatment. The control, fomesafen, caused a small increase in expression of *Cyp2b10* (6.09-fold) following 10 days of treatment. All other increases were minor and/or unrelated to dose.

TABLE 10. CAR/PXR signaling (fold increase)[a]

Gene	Oxyfluorfen (ppm)					Controls[b]	
	0	40	200	800	1600	Clofibric acid[c]	Fomesafen[c]
3-Day Treatment							
Cyp2b10	1	1.26	4.75	14.78	67.45	1.19	2.46
Alas1	1	2.21	1.89	3.17	14.10	1.57	2.52
Cyp3a11	1	-1.49	1.03	1.14	3.17	-1.25	-1.25
NADPH (Por)	1	-1.22	-1.25	1.18	2.13	1.95	2.23
10-Day Treatment							
Cyp2b10	1	1.70	8.29	26.01	38.67	2.63	6.09
Alas1	1	3.23	-1.21	2.80	15.26	-1.35	2.05
Cyp3a11	1	-1.25	1.15	1.31	1.90	-2.63	-1.67
NADPH (Por)	1	-1.67	-1.82	-1.64	1.23	-1.56	1.59

a Data were obtained from Text Table 4 on page 30 of the study report. fold = $2^{-\Delta\Delta Ct}$
b A positive control with phenobarb was not provided.
c Clofibric acid was administered at 1500 ppm. d Fomesafen was administered at 100 ppm
CAR = Constitutive androstane receptor PXR = Pregnane X receptor

V. MODE OF ACTION

This evaluation of the proposed modes of action follows the framework analysis described in the Final Guidelines for Carcinogen Risk Assessment (USEPA 2005), Klaunig et al. (2003), Cohen et al (2004), and Boobis et al (2006). This approach assesses 1) whether the weight of evidence is sufficient to establish the mode of action (MOA) in animals, 2) whether key events in the animal MOA are plausible in humans, 3) taking into account kinetic and dynamic factors, whether the animal MOA is plausible in humans, and 4) concludes with a statement of confidence and implications. Alternative modes of action should also be evaluated.

The registrant evaluated several modes of action and proposed that two MOAs are involved for oxyfluorfen: an MOA involving activation of PPARα (peroxisome proliferator-activated receptor alpha) and CAR (constitutive androstane receptor).

1. Evaluation of MOA involving activation of PPARα

The PPARα MOA was evaluated because oxyfluorfen has *some* structural similarity to other diphenyl ether herbicides which are recognized as PPARα agonists causing liver tumors in mice. (It should be noted, however, that one of the key structural features of potent PPARα agonists---the presence of a carboxylic acid moiety--is missing in oxyfluorfen (see SAR section)) These key events were evaluated: PPARα activation, induction of cell growth regulatory genes (gene expression induction), increased hepatocyte cell growth (increased cell proliferation and/or decreased apoptosis, temporal in normal hepatocytes and sustained in preneoplastic foci), selective clonal expansion of preneoplastic foci, and progression to neoplasia.

Following is a discussion of the key causal and associated events for the proposed PPARα MOA. Table 11 summarizes the key events and dose/temporal concordance necessary to establish a mode of action for hepatocarcinogenesis involving activation of the PPARα.

Activation of PPARα: The registrant conducted a reporter assay in rat hepatoma cells (MRDI 47835802) which was negative at a maximally soluble concentration. An article in the open literature reported that oxyfluorfen, as well as acifluorfen were negative for PPARα agonist activity in monkey kidney cells (Takeuchi, 2006). Neither of these assays were conducted in the appropriate mouse species which is required under the mode of action framework.

Expression of peroxisomal genes: Expression of PPARα genes was evaluated in mice dosed with 0, 40, 200, 800, or 1600 ppm oxyfluorfen and in mice dosed with the positive controls, 100 ppm fomesafen or 1500 ppm clofibric acid, for 3 or 10 days (MRID 47851601, 2009).

At 200 ppm and above, *Cyp4a10* expression was increased by 8.30- to 232.8-fold following 3 days of treatment, and was increased at 40 ppm and above by 3.70- to 240.6-fold following 10 days of treatment. At 800 ppm and above, *Cte-1* (cytosolic thioesterase 1) expression was increased by 7.11- to 14.46-fold following 3 days of treatment, and was increased at 200 ppm and above by 2.22- to 9.48-fold following 10 days of treatment. At 1600 ppm, *Acox1* (acyl CoA oxidase 1 or palmitoyl CoA oxidase) expression was increased by 4.63-fold and 3.39-fold after 3 and 10 days of treatment, respectively. Pmp-70 expression was similar to control at 200 ppm and 800 ppm (1.04 – 1.53 fold) and only slightly increased (2.24 fold) at 1600 ppm. The positive control, 100 ppm fomesafen, showed much greater increases than even the 1600 ppm oxyfluorfen groups.

Although *Acox1* was only upregulated at doses >200 ppm in the gene expression study, another study (MRID 46373101, 2003) found that Acyl CoA oxidase enzyme activity was increased 55% (non-significantly) at 200 ppm in comparison to controls and was increased 395% at 800 ppm after 28 days dosing.

PPARα-mediated expression of apoptosis: Apoptosis was not evaluated directly, but the anti-apoptotic gene, *Bcl-2,* and the proapoptic gene, *Bak-1,* were assessed in the gene expression study described above (MRID 47851601, 2009). No changes in the expression of either gene were observed in the treatment groups or in the positive controls.

Changes in lipid metabolism: Triglycerides were decreased 38% after 10 days of treatment but cholesterol was increased 26% (MRID 47851601, 2009). These effects occurred at a dose of 1600 ppm, much greater than the tumorigenic dose of 200 ppm. Oxyfluorfen thus shows an effect on lipid metabolism, but only at very high doses. However, most chemicals affecting peroxisomes cause decreased cholesterol which is inconsistent with the proposed mode of action for rodent liver tumors.

Peroxisome proliferation: Livers from 5 controls and 4 high-dose mice in a 28-day study (MRID 46373101, 2003) were examined by electron microscopy. Peroxisomes were variable in number in the different mice, but there was no increase in number, nor, presumably, volume. The increase in peroxisomal proliferation is a hallmark of this specific mode of action and is considered an associative key event.

Disruption of cell proliferation: S-phase DNA synthesis was evaluated in mice infused with BrdU for 28 days (MRID 46373101, 2003). S-phase DNA synthesis was increased 143% (non-significantly) at 200 ppm in comparison to controls and was increased 943% at 800 ppm.

The gene expression study described above (MRID 47851601, 2009) evaluated *c-Myc and Ccnd1* as markers of cell proliferation. After 3 days treatment with oxyfluorfen, *c-Myc* was upregulated in comparison to controls, but in a non-dose related manner (2-4 fold increase), which was comparable to the positive controls. After 10 days treatment, *c-Myc* was upregulated in the low- and high-dose groups (4.64 and 6.39 fold increase), but was not increased in the 2 mid-dose groups. The 100 ppm fomesafen group showed a greater increase at this time period (10.54 fold increase).

Hyperplasia was not seen microscopically. Hepatocellular hypertrophy and increased liver weight occurred in subchronic studies and the carcinogenicity study, but these are generic observations for any liver tumor formation.

Key events not assessed: Not tested were gap junction communication, hepatocyte oxidative stress, or Kupffer cell-mediated events.

Selective clonal expansion: Basophilic foci were not evaluated at the time that this study was conducted.

Table 11. Key events associated with the hepatocarcinogenesis involving activation of PPARα.

Key event	Evidence in animals	Dose Concordance	Temporal Concordance
Activation of PPARα	Negative, but tested in rats and not in mice.	- -	- -
Expression of peroxisomal genes	*Cyp4a10* gene expression weakly positive	**200 ppm**	3 and 10 days
	Cte-1 gene expression positive	800 ppm	3 and 10 days
	Acox1 weakly positive	1600 ppm	3 and 10 days
	Pmp-70 weakly positive	1600 ppm	3 and 10 days
	Acyl co-A oxidase activity increased	800 ppm	28 days
PPARα-mediated expression of cell cycle, growth, and apoptosis	Apoptosis not evaluated directly, but gene expression analysis for pro- and anti-apoptotic genes was negative.	- -	- -
Changes in lipid metabolism	Cholesterol increased instead of decreased	1600 ppm	11 days
Peroxisome proliferation	Not increased.	- -	- -
Disruption of cell proliferation	*c-myc* induction variably increased in different dose groups	- -	- -
	weak increase in S-phase DNA synthesis	**200 ppm**	28 days
	No hyperplasia	- -	- -
Inhibition of gap junction intercellular communication	Not required	- -	- -
Hepatocyte oxidative stress	No data provided (deficiency)	- -	- -
Kupffer cell-mediated events	Not required	- -	- -
Selective clonal expansion	No data. Basophilic foci not assessed in older studies.	- -	- -

Adapted from Klaunig, et al (2003).
Causal or associative key events with high specificity and a large weight of evidence in bold.

Uncertainties and Inconsistencies: There were many data voids and inconsistencies with the provided mode of action for rodent liver tumors. A clear inconsistency in this MOA is the lack of peroxisomes proliferating and increasing. Although the registrant proposed that increased peroxisomes were not seen because oxyfluorfen is a weak PPARα agonist, tumors were formed and these tumors should have followed the progressive list of key events identified in this mode of action and in keeping with the tumorigenic dose.

Another major weakness is that the reporter assay was negative for binding of oxyfluorfen to the PPARα receptor, which is a specific receptor ligand binding interaction that must occur before the cascade of key events follow towards the pathway of tumorigenicity. Added to this negative binding assay is that this study was conducted in rats, rather than mice, because the registrant reported that the assay in mice was not available.

Additionally, the cholesterol level was increased, rather than decreased, as is the case with most PPARα agonists. The registrant attributed the increased cholesterol to CAR activation.

Is the weight of evidence sufficient to establish a mode of action involving PPARα in animals?
As noted above, the only key event with dose concordance was a weak induction of *Cyp4a* and a weak increase in S-phase DNA synthesis. Peroxisomes were not increased and there was no evidence for activation of PPARα activation, hepatocyte oxidative stress, or selective clonal

expansion. Many of these observations are generic and applicable for many pathways leading to rodent liver tumors. The overall weight of evidence did not support a specific rodent liver mode of action involving activation of the PPARα receptor.

2. Evidence for a MOA involving activation of CAR

Following is a discussion of the key causal events for the proposed CAR (constitutive androstane receptor) MOA. Table 12 shows key events with dose and temporal concordance.

Activation of CAR: CAR activation is the critical initiating event but was not assessed.

Altered gene expression: CAR signaling was assessed by gene expression analysis of *Cyp2b10.* Treatment with oxyfluorfen caused a dose-related increase in upregulation of *Cyp2b10* at 200 ppm and above after 3 days (4.75- to 67.45-fold) and 10 days (8.29- to 38.67-fold) of treatment.

The CAR/PXR pathway was assessed with *Alas1, Cyp3a11, and NADPH (Por*). The latter genes were not affected, except for *Alas1* expression which was increased slightly at 800 ppm and above.

Suppression of apoptosis: Apoptosis was not evaluated directly, but the anti-apoptotic gene, *Bcl-2,* and the proapoptic gene, *Bak-1,* were assessed in the gene expression study described above (MRID 47851601, 2009). No changes in the expression of either gene were observed in the treatment groups or in the positive controls.

Increased cell proliferation: S-phase DNA synthesis was evaluated in mice infused with BrdU for 28 days (MRID 46373101, 2003). S-phase DNA synthesis was increased 143% (non-significantly) at 200 ppm in comparison to controls and was increased 943% at 800 ppm.

The gene expression study described above (MRID 47851601, 2009) evaluated *c-Myc and Ccnd1* as markers of proliferation. After 3 days treatment with oxyfluorfen, *c-Myc* was upregulated in comparison to controls, but in a non-dose related manner (2-4 fold increase), which was comparable to the positive controls. After 10 days treatment, *c-Myc* was upregulated in the low- and high-dose groups (4.64 and 6.39 fold increase), but was not increased in the 2 mid-dose groups. The 100 ppm fomesafen group showed a greater increase at this time period (10.54 fold increase).

Hyperplasia was not seen microscopically. Hepatocellular hypertrophy and increased liver weight occurred in subchronic studies and the carcinogenicity study.

Alteration in liver function: Triglycerides were decreased 38% after 10 days of treatment but cholesterol was increased 26% (MRID 47851601, 2009). These effects occurred at a dose of 1600 ppm, much greater than the tumorigenic dose of 200 ppm. Oxyfluorfen thus shows an effect on lipid metabolism, but only at very high doses.

Selective clonal expansion of preneoplastic foci and progression of preneoplastic foci to neoplasia: Basophilic foci were not evaluated at the time that this study was conducted.

Uncertainties and Inconsistencies: CAR activation is the critical initiating event but was not assessed.

The mouse cancer study was conducted with the older, 76% product, while the MOA studies were conducted with the newer, 97% product. However, the older product was much more toxic to rats when subchronic studies with 76% and 97% products are compared and when developmental studies in rats with 76% and 97% products are compared.

Table 12. Key events associated with the hepatocarcinogenesis involving activation of CAR.

Key event	Evidence in animals	Dose Concordance	Temporal Concordance
Activation of CAR	Not tested.	- -	- -
Altered Gene Expression	*Cyp2b10* weakly positive	200 ppm	3 and 10 days
Disruption of cell proliferation/apoptosis	*c-myc* induction variably increased in different dose groups	- -	- -
	Weak increase in S-phase DNA synthesis	200 ppm	28 days
	No hyperplasia	- -	- -
	Apoptosis not evaluated	- -	- -
Alteration in liver function	Only decreased triglycerides, increased cholesterol	1600 ppm	11 days
Selective clonal expansion	No data. Basophilic foci not assessed in older studies.	- -	- -

Is the weight of evidence sufficient to establish a mode of action involving CAR in animals?

There was no evidence for activation of CAR, the key initiating event. The only key event with dose concordance was a weak induction of *Cyp2b10* and a weak increase in S-phase DNA synthesis. The cell proliferation data did not demonstrate that the S-phase DNA synthesis was transient and not sustained, which is pivotal for a mitogenic mode of action. The overall weight of evidence did not support a mode of action involving activation of the PPARα receptor.

3. Other Modes of action

Cytotoxicity: A MOA for cytotoxicity was not supported by the data. The key events for cytotoxicity MOA are sustained cytotoxicity and regenerative proliferation at the carcinogenic dose. After 20 months, nearly half the male mice had single cell hepatocellular necrosis and increased cytomegaly and karyomegaly. By comparison, in the 90-day study, 2/15 rats had focal cell necrosis and after 28 days treatment in the MOA study, only 1/10 mice dosed at 200 ppm had liver necrosis. After 20 months, alkaline phosphatase (111% and 80%) and ALT (77% and 17%) were very slightly increased compared to untreated and ethanol controls, respectively. These 2 enzymes were not increased in the 90-day study. The cytotoxicity MOA was not supported by the data because there was not significant necrosis in the subchronic studies for durations of up to 90 days.

Porphyria: A MOA involving porphyria was not considered likely. Oxyfluorfen has the potential to induce porphyria at high doses because it inhibits protoporphyrinogen oxidase, the second-to-

last enzyme in heme biosynthesis. This MOA was rejected because the porphyria occurs at high doses (Norman Birchfield, personal communication).

Mutagenicity: A mutagenic mode of action was rejected. Mutagenicity studies with the new 97% a.i. were all negative. The only positive studies were with the older 71% a.i. which is no longer manufactured.

VI. WEIGHT-OF-THE EVIDENCE CONSIDERATIONS

- Oxyfluorfen treatment resulted in statistically significant trends for hepatocellular adenomas, carcinomas, and combined tumors compared to both concurrent control groups, and a statistically significant pair wise comparison for combined tumors in male CD-1 mice compared to the ethanol concurrent control group. The incidence for adenomas was within the historical control range for hyperplastic nodules (now classified as adenomas) but the incidence for carcinomas exceeded the historical control range for hepatocellular carcinomas. The CARC concluded that the liver tumors in male mice were treatment-related. Dosing was considered adequate but the animals could have tolerated a higher dose which might have resulted in a stronger tumor response.

- Dosing in the rat combined toxicity/carcinogenicity study was inadequate to assess carcinogenicity.

- There are no mutagenicity concerns for the currently registered oxyfluorfen product (>96% active ingredient).

- Oxyfluorfen is structurally related to 3 other diphenyl ether herbicides, fomesafen, acifluorfen, and lactofen, that cause liver tumors and which have been evaluated by the Cancer Assessment Review Committee. These 3 chemicals are considered to act by a mode of action involving activation of the PPARα (peroxisome proliferator-activated receptor alpha). However, oxyfluorfen differs from these compounds because the side chain of oxyfluorfen cannot be metabolized to a carboxylic acid, suggesting that oxyfluorfen is not expected to be a strong peroxisome proliferator and is not similar to fomesafen.

- A mode of action for the mouse liver tumors involving PPARα activation was evaluated. Oxyfluorfen was negative for PPARα activation when tested in rat tissue. Peroxisomes were not increased with oxyfluorfen treatment. There was a weak increase in *Cyp4a10* gene expression at the tumorigenic dose of 200 ppm. It was concluded that the overall weight of evidence did not support a mode of action involving activation of the PPARα receptor.

- A mode of action involving CAR was assessed. Activation of the receptor was not assessed but oxyfluorfen treatment caused weak activation of *Cyp2b10*. It was concluded that the overall weight of evidence did not support a mode of action involving activation of the PPARα receptor.

- A mode of action involving cytotoxicity was not supported by the data for the durations assessed in the subchronic toxicity studies. A mode of action involving porphyria was not supported at a tumorigenic dose.

VII. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC classified Oxyfluorfen as "Likely to be Carcinogenic to Humans". This classification was based on the occurrence of treatment-related hepatocellular tumors in male mice and the lack of an adequate carcinogenicity study in a second species (rat). Although there were no mutagenic concerns for oxyfluorfen, the data were inadequate to support a non-mutagenic mode of action for liver tumorigenesis.

The CARC suggests that the registrant consider submitting a chronic/cancer study in the rat as an alternative to additional mechanistic studies.

VIII. QUANTIFICATON OF CARCINOGENICITY

The Committee recommended that a linear low-dose quantitative approach (Q_1*) be retained for human risk characterization with extrapolation based on combined hepatocellular tumors in male mice.

APPENDIX

METABOLIC PATHWAY

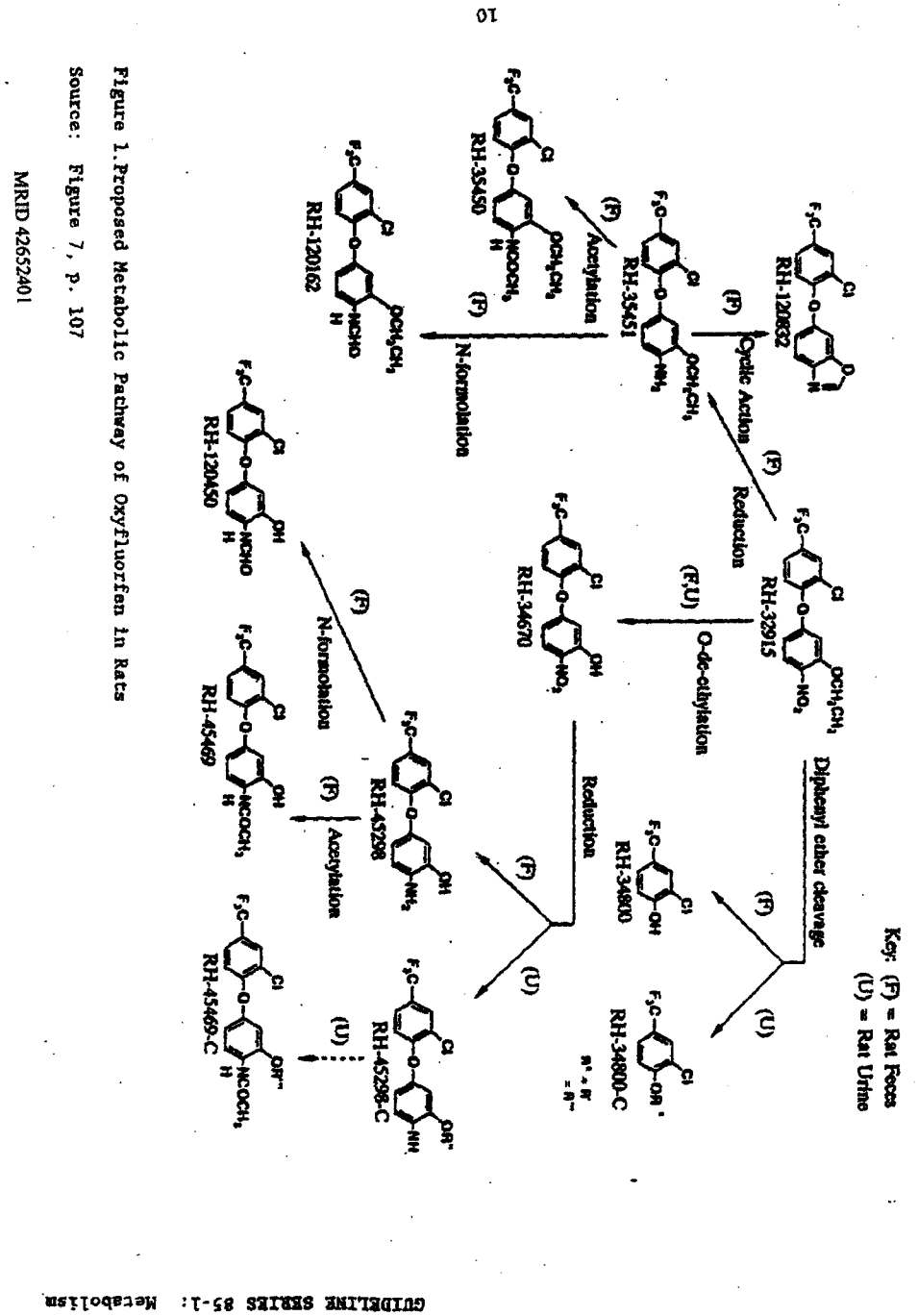


Figure 1.Proposed Metabolic Pathway of Oxyfluorfen in Rats

Source: Figure 7, p. 107

MRID 42652401

GUIDELINE SERIES 85-1: Metabolism

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